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<p>(21) International Application Number: PCT/SE98/01599 (22) International Filing Date: 9 September 1998 (09.09.98) (30) Priority Data: 9703407-8 19 September 1997 (19.09.97) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): BAUER, Carl-Axel [SE/SE]; Astra Draco AB, P.O. Box 34, S-221 00 Lund (SE). TROFAST, Jan [SE/SE]; Astra Draco AB, P.O. Box 34, S-221 00 Lund (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p>	
<p>(54) Title: NEW USE FOR BUDESONIDE AND FORMOTEROL</p> <p>(57) Abstract</p> <p>The invention provides the use of formoterol and budesonide in the treatment of chronic obstructive pulmonary disease.</p>		

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NEW USE FOR BUDESONIDE AND FORMOTEROL

Field of the Invention

The invention provides the use of formoterol and budesonide in the treatment of chronic
5 obstructive pulmonary disease (COPD).

Background to the Invention

Chronic obstructive pulmonary disease (COPD) is a term which refers to a large group of
10 lung diseases which can interfere with normal breathing. It is estimated that 11% of the
U.S. population has COPD and the incidence is increasing. The two most important
conditions covered by COPD are chronic bronchitis and emphysema.

Chronic bronchitis is a long-standing inflammation of the bronchi which causes increased
15 production of mucous and other changes. The patients' symptoms are cough and
expectoration of sputum. Chronic bronchitis can lead to more frequent and severe
respiratory infections, narrowing and plugging of the bronchi, difficult breathing and
disability.

20 Emphysema is a chronic lung disease which affects the alveoli and/or the ends of the
smallest bronchi. The lung loses its elasticity and therefore these areas of the lungs become
enlarged. These enlarged areas trap stale air and do not effectively exchange it with fresh
air. This results in difficult breathing and may result in insufficient oxygen being delivered
to the blood. The predominant symptom in patients with emphysema is shortness of
25 breath.

At present moderate to severe COPD is treated with a variety of monotherapies including
inhaled or orally administered bronchodilators, inhaled anti-cholinergic agents and orally
administered steroids, especially corticosteroids. The problem with these treatments is that
30 none of them is especially effective. For example, many patients with COPD have a

reversible component. Accordingly a new treatment is required for decreasing the intensity of exacerbations, thereby improving the lung function of patients suffering from COPD.

Description of the Invention

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It has surprisingly been found that the combination of formoterol and budesonide is effective in treating COPD.

The combination of budesonide and formoterol reduces the number of exacerbations of
10 COPD compared to the monotherapies using budesonide or formoterol, thereby improving the lung function of the patients. Thus, the combination of budesonide and formoterol will give greater compliance, greater efficacy, less exacerbations and/or better sleep.

The present invention also gives an increased compliance and efficacy and thereby quality
15 of life.

According to the invention there is provided the use of a composition comprising, in admixture or separately:

(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or
20 solvate thereof, or a solvate of such a salt;

(b) a second active ingredient which is budesonide; and
a molar ratio of the first active ingredient to the second active ingredient of from 1:2500 to 12:1,

in the manufacture of a medicament for use in the treatment of chronic obstructive
25 pulmonary disease.

The composition used in the invention optionally additionally comprises one or more pharmaceutically acceptable additives, diluents and/or carriers. The composition is preferably in the form of a dry powder, wherein the particles of the pharmaceutically active
30 ingredients preferably have a mass median diameter of less than 10 μm .

The invention also includes the use of a kit containing:

- (i) a vessel containing the first active ingredient;
 - (ii) a vessel containing the second active ingredient;
 - 5 (iii) a molar ratio of the first active ingredient to the second active ingredient of from 1:2500 to 12:1; and
 - (iv) instructions for the simultaneous, sequential or separate administration of the active ingredients to a patient in need thereof;
- in the manufacture of a medicament for use in the treatment of chronic obstructive
10 pulmonary disease.

A patient suffering from COPD can be treated by administering via inhalation a composition as defined above. Alternatively such a patient can be treated by administering via inhalation, simultaneously, sequentially or separately, (i) a dose of the first active
15 ingredient; and (ii) a dose of the second active ingredient. The molar ratio of the first active ingredient to the second active ingredient is from 1:2500 to 12. The doses can be provided to the patient for inhalation in dry powder form.

The invention further provides the use of budesonide and of formoterol in the manufacture
20 of a composition or a kit, as used in the invention, for use in the treatment of chronic obstructive pulmonary disease.

The first and second active ingredients of the kit used in the invention can be administered simultaneously, sequentially or separately to COPD. By sequential is meant that the first
25 and second active ingredients are administered one after the other. They still have the desired effect if they are administered separately but less than about 12 hours apart, preferably less than about 2 hours apart, more preferably less than about 30 minutes apart, and most preferably one immediately after the other.

30 The molar ratio of the first active ingredient to the second active ingredient is suitably from 1:555 to 2:1 and preferably from 1:150 to 1:1. The molar ratio of the first active ingredient

to the second active ingredient is more preferably from 1:133 to 1:6. The molar ratio of the first active ingredient to the second active ingredient can also be 1:70 to 1:4.

5 Preferably the amount of the first active ingredient used is preferably from 2 to 120 nmol (more preferably from 7 to 70 nmol). The amount of the second active ingredient used is preferably from 0.1 to 5 μmol (preferably 0.15 to 4 μmol) or from 45 to 2200 μg , more preferably from 65 to 1700 μg .

10 Throughout the specification, the amount of the first and second active ingredient used relate to unit doses unless explicitly defined differently.

Suitable physiologically acceptable salts of formoterol include acid addition salts derived from inorganic and organic acids, for example the chloride, bromide, sulphate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 15 4-chlorobenzoate, p-toluenesulphonate, methanesulphonate, ascorbate, acetate, succinate, lactate, glutarate, gluconate, tricarballylate, hydroxynaphthalene-carboxylate or oleate salts or solvates thereof. The first active ingredient is preferably formoterol fumarate, especially the dihydrate thereof.

20 When the first active ingredient is formoterol fumarate dihydrate, the amount of the first active ingredient used is suitably from 1 to 50 μg , more suitably from 3 to 30 μg .

Preferably the composition or kit used in the invention comprises unit doses of 6 μg of formoterol fumarate dihydrate and 100 μg of budesonide, or 4.5 μg of formoterol fumarate 25 dihydrate and 80 μg of budesonide, either of which is administered up to four times a day. Alternatively the composition or kit of the invention comprises unit doses of 12 μg of formoterol fumarate dihydrate and 200 μg of budesonide, or 9 μg of formoterol fumarate dihydrate and 160 μg of budesonide, either of which is administered once or twice a day.

More preferably the composition or kit used in the invention comprises unit doses of 6 μ g of formoterol fumarate dihydrate and 200 μ g of budesonide, or 4.5 μ g of formoterol fumarate dihydrate and 160 μ g of budesonide, either of which is administered up to four times a day. Alternatively the composition or kit of the invention comprises unit doses of
5 12 μ g of formoterol fumarate dihydrate and 400 μ g of budesonide, or 9 μ g of formoterol fumarate dihydrate and 320 μ g of budesonide, either of which is administered once or twice a day.

Most preferably the composition or kit used in the invention comprises unit doses of 6 μ g
10 of formoterol fumarate dihydrate and 400 μ g of budesonide, or 4.5 μ g of formoterol fumarate dihydrate and 320 μ g of budesonide, either of which is administered up to four times a day.

Preferably the active ingredient(s) are used in admixture with one or more pharmaceu-
15 tically acceptable additives, diluents or carriers, preferably in an amount of from 50 μ g to 25 mg per dose, more preferably in an amount of from 50 μ g to 10 mg, most preferably in an amount of from 100 to 2000 μ g per unit dose. Examples of suitable diluents or carriers include lactose, dextran, mannitol or glucose. Preferably lactose is used, especially as the monohydrate.

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One or more of the ingredients is preferably in the form of a dry powder, more preferably a finely divided powder, e.g. micronised dry powder, most preferably an agglomerated micronised dry powder. As an alternative to agglomeration, the finely divided active ingredients may be in the form of an ordered mixture with the pharmaceutically acceptable
25 additive, diluent or carrier. An ordered mixture comprises fine particles of an active ingredient in association with coarse particles or a mixture of coarse and finely divided particles of the pharmaceutically acceptable additive, diluent or carrier. The ingredients used in the invention can be obtained in these preferred forms using methods known to those of skill in the art. The particle size of the active ingredients is preferably less than
30 10 μ m.

Administration may be by inhalation orally or intranasally. The active ingredients are preferably adapted to be administered, either together or individually, from dry powder inhaler(s) (DPIs), especially Turbuhaler[®] (Astra AB), pressurised metered dose inhaler(s) (pMDIs), or nebuliser(s).

When the active ingredients are adapted to be administered, either together or individually, from pressurised inhaler(s), they are preferably in finely divided, and more preferably in micronised form. They may be dissolved or, preferably, suspended in a liquid propellant mixture. The propellants which can be used include chlorofluorocarbons, hydrocarbons or hydrofluoroalkanes. Especially preferred propellants are P134a (tetrafluoroethane) and P227 (heptafluoropropane) each of which may be used alone or in combination. They are optionally used in combination with one or more other propellants and/or one or more surfactants and/or one or more other excipients, for example ethanol, a lubricant, an anti-oxidant and/or a stabilising agent.

When the active ingredients are adapted to be administered, either together or individually, via nebuliser(s) they may be in the form of a nebulised aqueous suspension or solution, with or without a suitable pH or tonicity adjustment, either as a unit dose or multidose device.

The composition or kit used in the invention may optionally be administered as divided doses from 1 to 4, and preferably once or twice a day.

The invention is illustrated by the following Examples which are not intended to limit the scope of the application. In the Examples micronisation is carried out in a conventional manner such that the particle size range for each component is suitable for administration by inhalation. Turbuhaler is a trademark of Astra AB.

Example 1

6 Parts by weight of formoterol fumarate dihydrate was mixed with 794 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 200 Parts by weight of micronised
5 budesonide was added to the conditioned product by mixing and homogenising with a low pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 2

10 4.5 Parts by weight of formoterol fumarate dihydrate was mixed with 835 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 160 Parts by weight of micronised budesonide was added to the conditioned product by mixing and homogenising with a low pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331
15 and filled into the storage compartment of a Turbuhaler.

Example 3

12 Parts by weight of formoterol fumarate dihydrate was mixed with 588 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then
20 conditioned using the process of EP-A-717 616. 400 Parts by weight of micronised budesonide was added to the conditioned product by mixing and homogenising with a low pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

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Example 4

6 Parts by weight of formoterol fumarate dihydrate was mixed with 894 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 100 Parts by weight of micronised budesonide was added to the conditioned product by mixing and homogenising with a low

pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 5

5 4.5 Parts by weight of formoterol fumarate dihydrate was mixed with 915 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 80 Parts by weight of micronised budesonide was added to the conditioned product by mixing and homogenising with a low pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331
10 and filled into the storage compartment of a Turbuhaler.

Example 6

12 Parts by weight of formoterol fumarate dihydrate was mixed with 788 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then
15 conditioned using the process of EP-A-717 616. 200 Parts by weight of micronised budesonide was added to the conditioned product by mixing and homogenising with a low pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 7

20 6 Parts by weight of formoterol fumarate dihydrate was mixed with 994 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.
25 200 Parts by weight of micronised budesonide was mixed with 800 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 8

4.5 Parts by weight of formoterol fumarate dihydrate was mixed with 995 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised
5 using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

160 Parts by weight of micronised budesonide was mixed with 840 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then
10 conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 9

12 Parts by weight of formoterol fumarate dihydrate was mixed with 988 parts by weight of
15 lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

400 Parts by weight of micronised budesonide was mixed with 600 parts by weight of
20 lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 10

25 6 Parts by weight of formoterol fumarate dihydrate was mixed with 994 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

100 Parts by weight of micronised budesonide was mixed with 900 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

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Example 11

4.5 Parts by weight of formoterol fumarate dihydrate was mixed with 995 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

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80 Parts by weight of micronised budesonide was mixed with 920 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

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Example 12

12 Parts by weight of formoterol fumarate dihydrate was mixed with 988 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

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200 Parts by weight of micronised budesonide was mixed with 800 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

25

Example A

Patients suffering from COPD are first put through a run-in period of 2 weeks and are then split into 4 groups of approximately equal numbers. Each group is then given either
5 budesonide/formoterol, budesonide alone, formoterol alone or placebo for a period of 12 months.

The following parameters for each patient are monitored throughout: mild and severe exacerbations, FEV₁ (forced expiratory volume in one second), vital capacity (VC), peak
10 expiratory flow (PEF), symptom scores and Quality of Life. Of these, mild and severe exacerbations are considered to be primary efficacy variables, whereas the remaining parameters are considered to be secondary efficacy variables.

Claims

1. Use of a composition comprising, in admixture or separately:
 - (a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or
5 solvate thereof, or a solvate of such a salt;
 - (b) a second active ingredient which is budesonide; anda molar ratio of the first active ingredient to the second active ingredient of from 1:2500 to 12:1,
in the manufacture of a medicament for use in the treatment of chronic obstructive
10 pulmonary disease.
2. Use according to claim 1, wherein the composition comprises one or more pharmaceutically acceptable additives, diluents and/or carriers.
- 15 3. Use of a kit containing:
 - (i) a vessel containing a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt;
 - (ii) a vessel containing a second active ingredient which is budesonide;
 - (iii) a molar ratio of the first active ingredient to the second active ingredient of from
20 1:2500 to 12:1; and
 - (iv) instructions for the simultaneous, sequential or separate administration of the first and second active ingredients to a patient in need thereof;in the manufacture of a medicament for use in the treatment of chronic obstructive
25 pulmonary disease.
4. Use according to claim 3, wherein the first and/or second active ingredient is used in admixture with one or more pharmaceutically acceptable additives, diluents and/or carriers.
5. Use according to any one of the preceding claims, wherein the first active ingredient is
30 formoterol fumarate dihydrate.

6. Use according to any one of the preceding claims, wherein the molar ratio of the first active ingredient to the second active ingredient is from 1:555 to 2:1, preferably from 1:70 to 1:4.
- 5 7. Use of formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt in the manufacture of a composition as defined in claim 1 or 2 or a kit as defined in claim 3 or 4 for use in the treatment of chronic obstructive pulmonary disease.
8. Use of budesonide in the manufacture of a composition as defined in claim 1 or 2 or a
10 kit as defined in claim 3 or 4 for use in the treatment of chronic obstructive pulmonary disease.
9. A method for the treatment of a patient suffering from chronic obstructive pulmonary disease which method comprises administering to the patient via inhalation,
15 simultaneously, sequentially or separately, a therapeutically effective amount of (i) a dose of a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt; and (ii) a second active ingredient which is budesonide, and wherein the molar ratio of the first active ingredient to the second active ingredient is from 1:2500 to 12:1.
20
10. A method for the treatment of a patient suffering from chronic obstructive pulmonary disease which method comprises administering to the patient via inhalation a therapeutically effective amount of a composition as defined in claim 1 or 2.

1
INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/01599

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/57 // (A61K 31/57, 31:165)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Schweiz Med Wochenschr, Volume 127, 1997, C. Wyser et al, "Neue Aspekte in der Behandlung des Asthma bronchiale und chronisch obstruktiver Lungenkrankheiten" page 885 - page 890 --	1-8
X	WO 9311773 A1 (AKTIEBOLAGET ASTRA), 24 June 1993 (24.06.93) -- -----	1-8

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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| <p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> | <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p> |
|--|---|

Date of the actual completion of the international search

Date of mailing of the international search report

22 December 1998

07 -01- 1999

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/01599

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 9-10
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

01/12/98

International application No.
PCT/SE 98/01599

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9311773 A1	24/06/93	AU 673660 B	21/11/96
		AU 3085892 A	19/07/93
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		HR 921445 A	31/12/94
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